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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/727,918	12/04/2003	Stephen P. Americ	3613/1/US	7539

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EXAMINER	
SIMMONS, CHRIS E	
ART UNIT	**PAPER NUMBER**
1609	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/727,918	ARNERIC, STEPHEN P.	
	Examiner	Art Unit	
	Chris E. Simmons	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57* is/are pending in the application.

4a) Of the above claim(s) *11-21,24-26,29-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10, 22-23, 27-28, 31-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/05/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group VI in the reply filed on 02/27/2007 is acknowledged.

2. Claims 11-21, 24-26 and 29-30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Election of invention VI and species election of celecoxib and pain was made **without** traverse in the reply filed on 02/27/2007.

Priority

Applicant's claim for the benefit of a prior-filed provisional application 60/433780 12/17/2002 is acknowledged. Applicant's claim for this benefit is granted.

Specification

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (p. 3, lines 25, 27 28. p. 53 line 1). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

> art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-10, 22-23, 27-28, and 31-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for alleviating or slowing the appearance of pain and/or inflammation associated with certain disorders or diseases disclosed in instant application (e.g., osteoarthritis, rheumatoid arthritis, headache, neuropathy, and some others), does not reasonably provide enablement for treating (as defined by Applicant), preventing or eliminating any disease disclosed in instant application. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant claims a method for the treatment, prevention, or inhibition of a CNS disorder, pain and inflammation, or an inflammation-associated disorder in a subject in need of such treatment, prevention, or inhibition, comprising administering a cyclooxygenase-2 selective inhibitor or prodrug thereof and reboxetine to the subject. However, in Applicant's specification in paragraph 462, Applicant states:

> [462] "The terms "treating" or "to treat" means to alleviate symptoms, eliminate the causation either on a temporary or permanent basis, or to prevent or slow the appearance of symptoms. The term "treatment" includes alleviation, elimination of causation of or prevention of pain and/or inflammation associated with, but not limited to, any of the diseases or disorders described above. Besides being useful for human treatment, these combinations are also useful for treatment of mammals, including horses, dogs, cats, rats, mice, sheep, pigs, etc."

The test of enablement requires a determination of whether the disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. That

standard is still the one to be applied. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

Unpredictability of the art. The art with regard to treating pain and/or inflammation associated with any disease is unpredictable. Essentially, a skilled artisan would need to practice trial and error experimentation of administering the claimed composition to subjects with randomly selected diseases associated with pain and inflammation.

Scope of the claims. The claims are broad and read on thousands of diseases with different pathological pathways.

State of the art. The art in the field of pain an inflammation management has not developed to the level in which pharmaceuticals can eliminate the cause on a permanent basis of inflammatory-associated diseases, CNS disorders, pain, or inflammation.

Given the analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have to conduct undue and excess experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 1-2, 6-10, 22-23, 27-28, 31, 35-36, 39, 45-50, and 52-57 are rejected under 35 U.S.C. 102(e) as being anticipated by Muller (U.S. Patent Application 10/157,969 -- herein referred to as '969), as evidenced by Penning et al. (J. Med. Chem., 40 (9), 1347 -1365, 1997).

The instant claims read on a method for the treatment, prevention, or inhibition of a CNS disorder, pain and inflammation, or an inflammation-associated disorder in a subject, comprising administering a cyclooxygenase-2 selective inhibitor or prodrug thereof and reboxetine.

'969 teaches a method for the prevention, treatment, or inhibition of a psychiatric (CNS) disorder such as tic, autism, and in particular schizophrenia (defined as having an inflammatory/immunological association in ¶ 7, ¶ 11-12 ¶ 338-339), which comprises administering a cyclooxygenase-2 selective inhibitor (celecoxib – defined in ¶ 271, ¶ 273, ¶ 334 – 336, and claims 16-18) or prodrug thereof and an antidepressant (reboxetine – defined in claims 24 and 33 and ¶ 351) in therapeutically effective

amounts (claim 30). (See abstract; ¶ 18; claims 12-37). '969 teaches the composition of the antidepressant and COX-2 selective inhibitor, comprising a pharmaceutically acceptable excipient and also teaches a suitable kit with 2 dosage forms comprising COX-2 selective inhibitor in one dosage form and the antidepressant in the other (¶ 360-361)

As for claims 6-10, the limitations are inherent properties of the Cox-2 selective inhibitor, celecoxib. Penning et al. (J. Med. Chem., 40 (9), 1347 -1365, 1997) teaches the IC_{50} values for celecoxib. It states In Table 1 (page 1351) that compound 1i (defined as celecoxib in last paragraph of *Introduction* on page 1347) has an IC_{50} of 15 mcM for COX-1 and 0.04 mcM for COX-2. In instant application in ¶ 96, Applicant states that selectivity ratio of COX-2 inhibition over COX-1 inhibition is calculated by dividing IC_{50} for COX-1 by IC_{50} for COX-2. Therefore selectivity for said ratio for celecoxib is 15 mcM/.04 mcM = 375.

As for claims 35-36, it is well known and is commonly practiced by those of ordinary skill in the art to calculate the recommended daily dosage of a pharmaceutical by dividing the total daily dosage (mg/day) by the weight of an average adult, which is 70 kg (sometime 60 kg is used). '969 teaches the COX-2 inhibitor amount may range from 50-1600 mg/day, preferably 200-600, more preferably 400 mg (¶ 355). And 400 mg per day divided by 70 kg is 5 mg/kg per day and consequently anticipates instant claims 35-36. If 60 kg is used then the amount would be 6.67 mg/kg per day which also anticipates instant claims.

8. Claims 40-43 and 51 are rejected under 35 U.S.C. 102(b) as being anticipated by Murdock et al. (09/754500 – herein referred to as '500).

'500 teaches in its abstract a composition comprising an amine-containing compound (antidepressant/reboxetine; ¶ 7 and 33) and an agent which enhances the activity of said compound (anti-inflammatory compound/celecoxib; ¶ 9) to relieve pain (osteoarthritis; ¶ 22) or various forms of tissue injury (¶ 22).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. Claims 3-5, 32-34 and 37-38 are rejected under 35 USC 103(a) as being unpatentable over Muller (U.S. Patent Application 10/157,969 – herein referred to as

'969) in view of Raggi et al. (Electrophoresis 2002, 23, 1870–1877 – herein referred to as Raggi).

'969 teaches a method for the prevention, treatment, or inhibition of a psychiatric (CNS) disorders such as tic, autism, and in particular schizophrenia (defined as having an inflammatory/immunological association in ¶ 7, ¶ 11-12 ¶ 338-339), which comprises administering a cyclooxygenase-2 selective inhibitor (celecoxib – defined in ¶ 271, ¶ 273, ¶ 334 – 336, and claims 16-18) or prodrug thereof and an antidepressant (reboxetine – defined in claims 24 and 33 and ¶ 351) in therapeutically effective amounts (claim 30). (See abstract; ¶ 18; claims 12-37).

'969 does not disclose expressly reboxetine as a racemic mixture, or an R isomer or an S isomer of reboxetine. '969 does not disclose expressly the amount of reboxetine within the range of about 2 mg/day to about 8 mg/day.

Raggi discloses advantages and disadvantages of R and S chiral enantiomers and racemic mixture. Raggi discloses dosage amounts of 4-8mg/day.

As for claim 3, at the time of the invention it would have been obvious to a person of ordinary skill in the art to use a racemic mixture of reboxetine in a composition of reboxetine and a COX-2 inhibitor.

The suggestion/motivation for doing so would have been to make the composition by a less expensive method using the commercially available racemic formulation provided by its manufacture (Raggi, last paragraph on page 1870) than it would be to separate it into its enantiomers (Raggi, 1st column last paragraph on page 1877).

As for claim 4, at the time of the invention it would have been obvious to a person of ordinary skill in the art to use an R isomer of reboxetine in a composition of reboxetine and a COX-2 inhibitor.

The suggestion/motivation for doing so would have been to increase bioavailability of reboxetine since the C_{max} (maximum plasma concentration) and AUC (area under the time-concentration curve) of (R,R)-reboxetine are more than double those of (S,S)- reboxetine and it is the pure form of the drug than the racemic mixture (Raggi, last paragraph on page 1870) .

As for claim 5, at the time of the invention it would have been obvious to a person of ordinary skill in the art to use an S isomer of reboxetine in a composition of reboxetine and a COX-2 inhibitor.

The suggestion/motivation for doing so would have been because of the data that show the (S,S)-enantiomer is a more potent norepinephrine reuptake inhibitor than the (R,R)-reboxetine and it is the pure form of the drug than the racemic mixture (Raggi, 1st paragraph on page 1871).

As for claims 32-34 and 37-38, at the time of the invention it would have been obvious to a person of ordinary skill in the art to use a dosage of reboxetine ranging between 4-8 mg/day (Raggi; (¶ 1 under *Introduction*) with the most preferable amount of 400 mg/day of a COX-2 inhibitor ('969; ¶ 355). This is a COX-2:reboxetine ratio ranging from 50:1 to 100:1.

The suggestion/motivation for doing so would have been to use an effective amount of reboxetine at very low doses (4–8 mg/day) to decrease chances of side effects (Raggi, 1st paragraph under *Introduction*).

Therefore it would have been obvious to combine '969 with Raggi to obtain the claimed invention as specified in claims 3-5 and 32-34 and 37-38.

12. Claim 44 is rejected under 35 USC 103(a) as being unpatentable over Muller (U.S. Patent Application 10/157,969 -- herein referred to as '969.

'969 teaches that COX-2 inhibitors are effective in treating rheumatoid arthritis (¶14). '969 also teaches on a method for the prevention, treatment, or inhibition of a psychiatric (CNS) disorders such as tic, autism, and in particular schizophrenia (defined as having an inflammatory/immunological association in ¶ 7, ¶ 11-12 ¶ 338-339), which comprises administering a cyclooxygenase-2 selective inhibitor (celecoxib – defined in ¶ 271, ¶ 273, ¶ 334 – 336, and claims 16-18) or prodrug thereof and an antidepressant (reboxetine – defined in claims 24 and 33 and ¶ 351) in therapeutically effective amounts (claim 30). (See abstract; ¶ 18; claims 12-37).

'969 does not expressly teach the treatment of rheumatoid arthritis using the composition of a COX-2 inhibitor and reboxetine.

However, '969 does teach that rheumatoid arthritis is an inflammation-related disorder (¶13).

At the time of the invention it would have been obvious to a person of ordinary skill in the art to use reboxetine and a COX-2 inhibitor to treat rheumatoid arthritis.

The motivation for doing so would have been to enhance the ability of COX-2 to treat rheumatoid arthritis and associated pain.

Double Patenting

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-57 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-68 of copending Application No. 10/727717 (herein referred to as '717) in view of Raggi et al. (Electrophoresis 2002, 23, 1870–1877 – herein referred to as Raggi).

The instant application reads on a method for the treatment, prevention, or inhibition of a CNS disorder, pain and inflammation, or an inflammation-associated disorder in a subject in need of such treatment, prevention, or inhibition, comprising administering a cyclooxygenase-2 selective inhibitor or prodrug thereof and the antidepressant, reboxetine (a norepinephrine reuptake inhibitor -- NRI) to the subject

'717 discloses a method for the treatment, prevention, or inhibition of a CNS disorder, pain and inflammation, or an inflammation-associated disorder in a subject in need of such treatment, prevention, or inhibition, comprising administering a cyclooxygenase-2 selective inhibitor or prodrug thereof and a compound selected from the group consisting of duloxetine, venlafaxine and atomoxetine (also antidepressants that are NRIs in addition to being serotonin selective reuptake inhibitors -- SSRIs) to the subject. '717 also discloses that NRIs can be substituted in place of duloxetine, venlafaxine and atomoxetine (¶ 14).

'717 does not disclose expressly reboxetine or the specific dose ranges in instant claims 32-34. '717 does not expressly disclose the ratio/percentages in claims 37 and 38.

Raggi discloses that reboxetine is an NRI antidepressant and that the effective dose range is 4-8 mg/day (¶ 1 under *Introduction*) in composition with the most preferable amount of 400 mg/day of a COX-2 inhibitor ('969; ¶ 355). This is a COX-2:reboxetine ratio ranging from 50:1 to 100:1.

Claims 37 and 38 of instant application are obvious over claims 37 and 38 of '717, respectively.

It is the normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.

A prima facie case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art.

'717 and Raggi are analogous art because they are from a similar problem solving area. viz treating a CNS disorder, pain and inflammation, or an inflammation-associated disorder comprising administering a cyclooxygenase-2 selective inhibitor or prodrug thereof and an antidepressant.

At the time of the invention it would have been obvious to a person of ordinary skill in the art to substitute in place of duloxetine, venlafaxine and atomoxetine.

The suggestion/motivation for doing so would have been due to the fact that because reboxetine has such high selectivity for inhibiting the reuptake of norepinephrine, it is effective at very low dosages (4-8 mg/day) (Raggi ¶ 1 under *Introduction*).

Therefore it would have been obvious to combine Raggi with '717 to obtain the claimed invention as specified in claims 1-57.

This is a **provisional** obviousness-type double patenting rejection.

Conclusion

14. No claims are allowed.

15. It is noted that the following is pertinent art in relation to instant application:

- U.S. Patent 5,800,385
- U.S. Patent 6,096,742
- U.S. Patent 6,191,126 B1
- U.S. Patent 6,307,047 B1
- US Application 2001/0036943 A1
- 08/648113
- WO/00/24719

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chris E. Simmons whose telephone number is (571) 272-9065. The examiner can normally be reached on Monday - Friday from 7:30 - 5:00 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecelia Tsang can be reached on (571) 272-1600. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Chris Simmons/CES

CECILIA TSANG
SUPERVISORY PATENT EXAMINER